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Compensatory changes in eye growth and refraction induced by daily wear of soft contact lenses in young marmosets

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Abstract

Several studies have shown that growth of the primate eye responds in a compensatory direction to both positive and negative *spectacle* lenses — eyes grow more slowly and become hyperopic in response to positive lenses, and eyes grow more rapidly and become myopic in response to negative lenses. On the other hand, extended wear soft contact lenses, whether positively or negatively powered, induce hyperopia (Hung & Smith, 1996. Extended-wear, soft, contact lenses produce hyperopia in young monkeys. *Optometry & Vision Science 73*, 579–584.). We investigated whether responses in a compensatory direction occurred to soft contact lenses worn on a *daily wear basis* (8 h per day on an 8:16 h light:dark cycle). Ten infant marmosets (8–13 weeks of age) wore a soft contact lens, in one eye only, for 5–9 weeks. Lens powers used were zero ($n = 2$), +2D ($n = 1$), +2D followed after 5 weeks of lens wear by +4D ($n = 1$) for 4 weeks, +4D ($n = 2$), −2D followed after 5 weeks of lens wear by −4D ($n = 2$) for 4 weeks, −4D ($n = 2$). At the end of the lens-wear period the positive lens-wearing eyes were more hyperopic relative to the fellow untreated eyes [mean $+2.39 \pm 0.24$D (SE)] and the negative lens-wearing eyes were more myopic than the fellow untreated eyes [mean -2.48 ± 0.91D (SE)]. Fellow eyes were unaffected by lens wear [mean final refraction $+0.45 \pm 0.09$D (SE)]. Plano lenses did not affect eye growth in either marmoset fitted with plano contact lenses.

Keywords: Hyperopia; Myopia; Soft contact lenses; Eye growth; Marmoset; Primates

1. Introduction

We have shown in the preceding paper (Whatham & Judge, 2001) that zero-power soft contact lenses worn by infant marmosets for 8 h per day do not affect corneal power, eye growth or refraction, whereas lenses worn continuously 24 h per day cause corneal flattening, alteration of eye growth and a hyperopic shift in refraction, as they do in the macaque (Hung & Smith, 1996). The present paper builds on the above result by investigating the effect of powered soft contact lenses worn 8 h per day, and removed for an extended night period of the remaining 16 h per day, on eye growth. The main aim of these experiments is to see whether, if this approach is used, the effects on ocular growth of contact lenses will become broadly similar to those of spectacle lenses, and so make feasible the use of contact lenses rather than spectacle lenses in future studies of the effect of altered optical demand on eye growth.

Powered spectacle lenses worn early in life have been shown to alter postnatal ocular development in infant non-human primates in studies by Hung, Crawford, and Smith (1995), Judge and Graham (1995), Smith and Hung (1999) and Graham and Judge (1999b). Hung et al. (1995) and Smith and Hung (1999) reared infant macaque monkeys wearing positive or negative powered spectacle lenses and found that positive-powered spectacle lenses slowed axial eye growth and caused hyperopic shifts in refraction whereas negative-powered spectacle lenses accelerated axial eye growth and cause myopic shifts in refractive errors. Moreover, if the lens powers were small (+ or −3D) the shift in refraction compensated fully for the presence of the lens, whereas with higher powered lenses (+ or −6D or more) compensation was at best partial and inconsistent.

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In the infant common marmoset *Callithrix jacchus*, a small New World primate, Judge and Graham (1995) and Graham and Judge (1999b) reported that negative-powered (-4D or -8D) spectacle lenses caused myopia and axial elongation (though compensation was incomplete over the short period of lens wear used — 4 weeks from the age of 4 weeks). Positive-powered lenses worn for the same period had little or no effect.

In contrast, contact lenses fitted to macaques on an extended wear basis (24 h per day) caused hyperopia whether the lenses were negative, positive or zero-powered (plano) (Crewther, Nathan, Kiely, Brennan, & Crewther, 1988; Chung, 1993; Smith, Hung, & Harwerth, 1994; Hung & Smith, 1996). Crewther et al. (1988) fitted 10 cynomolgus monkeys with soft contact lenses of either $+6$D, 0D, -6D or -9D, nine of whom wore a lens in one eye only. Lens-wear began between 7 and 46 weeks of age and continued for 15–67 weeks. At the end of the observation period four monkeys developed axial hyperopia ($+2.3$ — $+6.0$D) in the lens-wearing eye relative to the non lens-wearing eye. Two of these monkeys had worn $+6$D lenses and two had worn -6D lenses. Interocular differences in refractive error for the other monkeys at the end of the observation period did not exceed ± 1.0D. No responses to negative lenses were observed that were in a compensatory direction. There was also no consistent effect of lens wear on corneal curvature (both increases and decreases in corneal curvature were observed in the lens-wearing eyes relative to the control eyes), although the authors reported that keratometry was difficult to perform due to corneal dehydration under anaesthesia.

Chung (1993) also reported hyperopia in response to wear of both positive and negative soft contact lenses in young primates. Chung fitted equal-powered soft contact lenses to both eyes of nine infant cynomolgus macaques for a period of 6–57 weeks. Four monkeys wore $+10$D lenses, three wore -10D lenses and two wore plano lenses. At the end of the lens wear period the mean change in refraction since the onset of lens wear was $+4.50$D for the $+10$D monkeys, $+2.63$D for the -10D monkeys and $+0.75$D for the plano monkeys. Smith et al. (1994) also reported that hyperopia developed in response to wear of negative soft contact lenses. In their study five out of eight infant macaque monkeys fitted with a -9D soft contact lens in one eye developed axial hyperopia of 2.0–3.5D after 2–3 months of lens wear.

Hung and Smith (1996) used contact lens powers (± 3D) which were equivalent to the spectacle lens powers for which compensation was observed by Hung et al. (1995). Also, eyes that wore plano lenses developed substantial hyperopic shifts in refraction (3–6D) during the period of lens wear. It is therefore clear that the hyperopia induced by continuous wear of soft contact lenses cannot be attributed solely to the use of lens powers too large for reliable compensation (Hung & Smith, 1996; Smith & Hung, 1999).

This study also aims to conclusively establish a marmoset model of contact lens wear that can be used to further investigate the postnatal regulation of ocular growth and refractive development, and in particular, to address important issues, such as the susceptibility of *juvenile* eye growth to altered optical demand that may not be feasible using spectacle lenses.

2. Methods

2.1. Subjects

Ten infant marmosets (*Callithrix jacchus*) ranging in age from 56–94 days of age wore a soft contact lens in one eye only, for a period of 35–64 days. Marmosets were fitted with one of the following lenses: plano lenses ($n=2$), $+2$D lenses ($n=2$), $+4$D lenses ($n=2$), -2D lenses ($n=2$) or -4D lenses ($n=2$). After 5 weeks of lens wear the -2D lenses were replaced by -4D lenses for the remainder of the lens wear period (4 weeks) in both -2D lens-wearing marmosets, and the $+2$D lens was replaced by a $+4$D lens after 5 weeks of lens wear in one marmoset (Fe) for the remainder of the lens wear period (4 weeks). The other $+2$D lens-wearing marmoset (Gr) wore a $+2$D lens for the whole of the lens wear period. All marmosets were raised in family groups under a daily light:dark cycle of 8:16 h. Cycloplegic retinoscopy was performed in all marmosets (awake) both with and without the soft contact lenses in place to verify that the contact lenses produced the required change in the refractive state of the eye. In all marmosets refractive state did not change by more than ± 0.50D from the nominal refractive power of the contact lens in air, after the contact lens was inserted into the eye.

2.2. Contact lens wear

Marmosets were fitted with soft contact lenses (77% water content), specially designed for the small eye of the marmoset (Ultravision International, UK) as described in Whatham and Judge (2001). Marmosets wore contact lenses in a daily wear regime in which the lenses were only worn for 8 h each day, for the full duration of the light period. Contact lenses were not worn on an extended wear basis because plano lenses worn continuously by marmosets have been shown to cause corneal flattening and hyperopia whereas plano lenses worn for 8 h per day did not produce any hyperopia or corneal flattening (Whatham & Judge, 2001).

At the onset of the light period the marmosets were removed from their cages and the contact lenses were inserted immediately into their eyes. Eight hours after the lenses were inserted the lights were removed and the illumination switched off. There were only brief periods at the beginning and end of the light period (before the lenses were inserted and after they were removed) when the lights were on but no lenses were worn. In our experience contact lenses could be inserted within several minutes after the onset of illumination each day by an experienced optometrist (AW) and removed within 1 minute, such that the total time lenses were not in the eye while the lights were on was < 8 min per day ($< 2\%$ of the light period).

Corneal health was checked regularly before, during and after the period of lens wear using a direct ophthalmoscope with and without the aid of fluorescein as described in Whatham and Judge (2001).

2.3. Optometric measurements

The marmosets were fully anaesthetised for all optometric measurements using 0.9% alphaxalone and 0.3% alphadolone acetate [Saffan, Pittman-Moore, UK, 12 mg/kg i.m. (weight < 100 g) or 18 mg/kg i.m. (weight > 100 g)]. Refractive error was measured by cycloplegic retinoscopy, following topical administration of 1–2 drops of 1% cyclopentolate hydrochloride (Chauvin Pharmaceuticals, UK), and axial ocular dimensions were measured using A-scan ultrasonography (Ophthasonic A-Scan III, Mentor, USA). In accordance with the protocol used by Graham and Judge (1999a) four retinoscopy measurements were made in each eye — two in the horizontal meridian and two in the vertical meridian (which were averaged to a mean value) for measures of refractive error. Retinoscopy measurements were corrected for working distance but NOT for artefact of retinoscopy. Four individual axial ultrasound scans of the eye (four separate placements of the probe on the eye) were recorded and averaged for the measurement of axial ocular dimensions.

Corneal power was measured in all animals using the rigid contact lens technique described in Whatham and Judge (2001). In brief, retinoscopy was performed through each eye of anaesthetised marmosets both with and without a zero-powered rigid contact lens of known base curve placed on the eye. The difference between these two readings was taken to be equivalent to the tear lens power. Corneal curvature (and corneal power) were calculated from the tear lens power using the formulae derived in Whatham and Judge (2001).

3. Results

3.1. Lens wear

Table 1 contains information relating to the lens wear compliance for the 10 marmosets fitted with contact lenses. All marmosets, with the exception of Kr, wore lenses for $> 95\%$ of the lens wear period, which is comparable to that reported by Whatham and Judge (2001) and Fernandes, Tigges, Tigges, Gammon and Chandler (1988) for macaque monkeys. The one marmoset, Kr, that temporarily ceased lens wear for 4 days due to a swollen eyelid, still managed to achieve $> 85\%$ compliance.

Optometric measures of refractive error, vitreous chamber depth and corneal power (expressed as interocular differences: experimental eye — control eye) for the 10 marmosets fitted with contact lenses are shown in Figs. 1A, 2 and 3, respectively. These figures are plotted as interocular differences so that variation in starting values between individual animals does not obscure the main effects. The absolute refractive error of the untreated eyes for each group are shown in Fig. 1B. Table 2 shows the interocular differences in refractive error, vitreous chamber depth and corneal power for all marmosets at the end of the lens-wearing period.

At the onset of lens wear there were no significant interocular differences in refraction, corneal power or axial ocular dimensions [anterior segment depth (corneal thickness + anterior chamber depth), crys-

Table 1
Lens wear compliance

Name	Lens(es) (D)	Maximum wear time (h)	Lenses lost	Total time lost (h)	Actual lens wear period (%)
Ju	+4	488	3	20	95.9
Ly	+4	304	0	0	100
Fe	+2/+4	504	3	11.5	97.7
Gr	+2	504	4	14	97.2
He	Plano	280	1	8	97.1
Il	Plano	280	0	0	100
Cr	−2/−4	512	0	0	100
De	−2/−4	512	2	10	98
El	−4	496	2	6.5	98.7
Kr	−4	488[a]	5	65	86.7

[a] Indicates lens removed from eye for 4 days due to swollen upper lid.

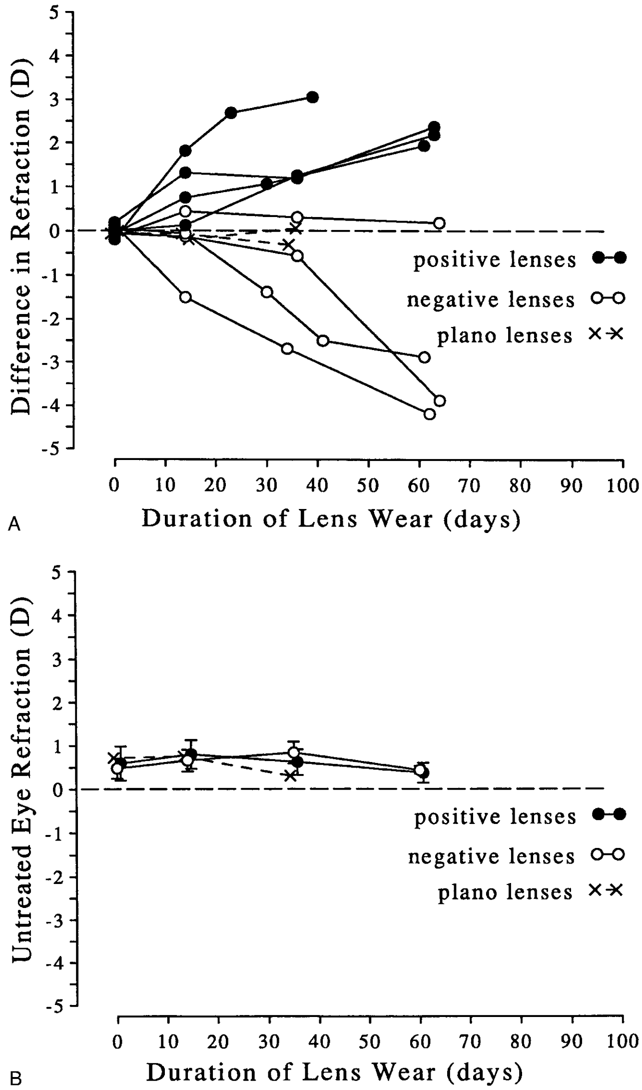

Fig. 1. A. Interocular difference in refraction (lens-wearing eye — control eye) throughout the period of lens wear for all marmosets. Refraction is in Dioptres and age is in days, plotted on a linear scale. The filled symbols represent data from the positive lens-wearing marmosets, the open symbols represent data from the negative lens-wearing marmosets and the crosses represent data from the plano lens-wearing marmosets. Eyes wearing positive lenses became hyperopic, and with one exception eyes wearing negative lenses became myopic, relative to the fellow eyes. Eyes wearing plano lenses remained approximately emmetropic. B. Refractive errors for the untreated eyes of all marmosets throughout the period of lens wear for all marmosets. Refraction is in Dioptres and age is in days, plotted on a linear scale. The filled symbols represent mean values for the positive lens-wearing marmosets ($n = 4$), the open symbols represent mean values from the negative lens-wearing marmosets ($n = 4$) and the crosses represent mean values ($n = 2$) from the plano lens-wearing marmosets. Error bars signify $\pm$ SE of measurement.

talline lens thickness or vitreous chamber depth] for the group of marmosets (paired t-test on all 10 marmosets: refraction $P = 0.74$, corneal power $P = 0.89$; anterior segment depth $P = 0.83$; lens thickness, $P = 0.43$; vitreous chamber depth $P = 0.24$). Changes in anterior segment depth and crystalline lens thickness were unremarkable throughout the period of lens-wear, therefore discussion of the effect of powered contact lens wear on axial ocular growth will be limited to changes in vitreous chamber depth.

3.2. Positive lenses

The two marmosets fitted with $+4$D lenses (Ly and Ju) developed hyperopic shifts in refraction at the end of just two weeks of lens wear (see Fig. 1A). These interocular differences in refraction increased during the lens wear period and were associated with interocular differences in vitreous chamber depth (see Fig. 2). At the end of the lens wear period the eyes that had worn the $+4$D lenses were $+1.9$D (Ju) and $+3.1$D (Ly) more hyperopic than their fellow untreated eyes (Table 2). The vitreous chambers of the lens-wearing eyes were 0.09 and 0.07 mm shorter than the vitreous chambers of the fellow eyes at the end of the lens wear period (see Table 2). The other marmosets (Fe and Gr) fitted with positive contact lenses for the duration of the lens wear period also developed a relative hyperopia in the lens-wearing eyes. The marmoset fitted with a $+2$D lens for the duration of the lens wear period (Gr) developed a hyperopia of $+2.4$D, relative to the fellow eye, after 63 days of lens wear (the end of the lens wear period) which was associated with a 0.12 mm shallower vitreous chamber (see Table 2). The remaining positive lens-wearing marmoset wore a $+2$D lens for the first 5 weeks of the lens-wearing period and then a $+4$D lens for the remaining 4 weeks. At the end of the lens wear period this marmoset had developed hyperopia of $+2.2$D and a 0.12 mm shallower vitreous chamber compared to the untreated fellow eye (see Table 2).

3.3. Negative lenses

Myopia was observed in three of the four marmosets fitted with negative contact lenses (open symbols in Fig. 1A), which was close to full compensation to the initial lens power (-4D) at the end of the period of lens wear. Myopia was first observed in the two marmosets fitted with -4D lenses throughout the period of lens wear (El and Kr) after 2 and 5 weeks of lens wear, respectively. The degree of myopia progressed in these marmosets throughout the period of lens wear and the lens-wearing eye was -4.2D (El) and -2.9D (Kr) more myopic than the fellow eye at the end of the lens wear period (see Table 2). These relative myopic refractive errors were associated with increased growth of the vitreous chamber of 0.29 and 0.18 mm, respectively. The remaining two marmosets fitted with negative contact lenses wore a -2D lens for the first 5 weeks of the lens wear period and a -4D lens for the final 4 weeks of the lens wear period. One of these marmosets (Cr) did not develop myopia and showed little interocular

Table 2
Optometric measures at the end of the lens wear period for all marmosets[a]

Name	Lens(es) (D)	Difference in CP (D)	Difference in VCD (mm)	Anisometropia (D)
Ju	+4	−0.19	−0.09	+1.94
Ly	+4	−0.69	−0.07	+3.06
Fe	+2/+4	−1.01	−0.12	+2.19
Gr	+2	−0.57	−0.12	+2.38
He	Plano	0.06	−0.03	−0.31
Il	Plano	−0.44	−0.03	+0.06
Cr	−2/−4	−0.62	0.10	+0.19
De	−2/−4	0.25	0.39	−3.88
El	−4	0.63	0.29	−4.19
Kr	−4	−0.06	0.18	−2.88

[a] Corneal power is abbreviated to CP and vitreous chamber depth to VCD. Optometric measures are expressed as interocular differences (treated eye — control eye).

difference in refraction (< 0.5D) at any point during the lens-wearing period while the other marmoset (De) developed myopia which had fully compensated to the final lens power (−4D) by the end of the lens wear period. At the end of the lens wear period the negative lens-wearing eye was −3.9D more myopic than the fellow untreated eye and had a 0.39 mm longer vitreous chamber (see Table 2). Therefore three of the four marmosets fitted with negative contact lenses developed myopia in the lens-wearing eye which approximately compensated for the final lens power by the end of the lens wear period (9 weeks after onset of lens wear).

The interocular differences in refraction and interocular differences in vitreous chamber depth at the end of the lens wear period are plotted in Fig. 4. Interocular differences in refraction were significantly correlated with interocular differences in vitreous chamber depth ($r = -0.93$, $P < 0.0001$).

3.4. Corneal effects

The interocular difference in corneal power in all marmosets throughout the lens wear period is shown in Fig. 3. There was a small degree of corneal flattening observed in the lens-wearing eyes, relative to the untreated fellow eyes throughout the lens wear period. At the end of the lens-wear period interocular differences in corneal power varied across all marmosets from 0.6 to −1.0D (Table 2) and did not exceed 1D in any marmoset during the lens-wear period (Fig. 3). The mean corneal power of all 10 lens-wearing eyes was 0.26 ± 0.16D (SE) less than that of the fellow untreated eyes, which was not statistically significant (paired t-test on corneal power at the end of the lens wear period in all 10 animals, $P = 0.06$). There was also no significant difference in corneal power, at the end of the lens-wear period, between eyes that wore positive lenses and eyes that wore negative lenses (unpaired t-test: $P = 0.08$).

3.5. Untreated eyes

The refractive error of marmosets fitted with positive lenses, negative lenses and plano lenses throughout the lens-wear period are shown in Fig. 1B. Refractive error and vitreous chamber depth of the untreated eyes of the positive lens-wearing marmosets ($n = 4$) were compared to the untreated eyes of the negative lens-wearing marmosets ($n = 4$) to determine whether there was any interocular effect of powered lens wear on ocular

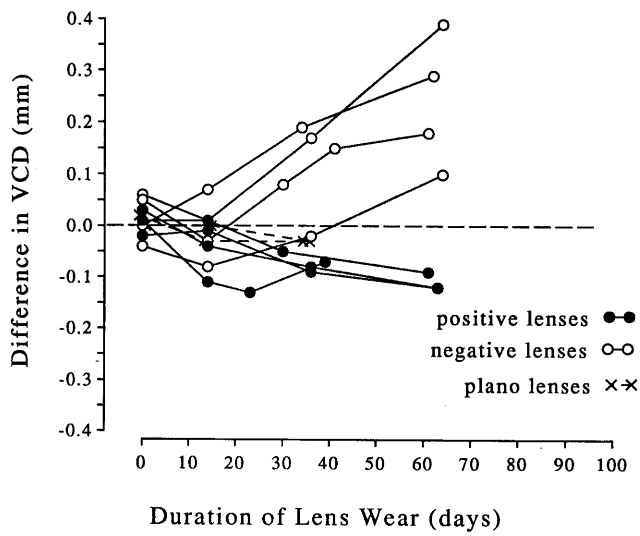

Fig. 2. Interocular difference (lens-wearing eye — control eye) in vitreous chamber depth (VCD) throughout the period of lens wear for all marmosets. Vitreous chamber depth is in millimetres and age is in days, plotted on a linear scale. The filled symbols represent data from the positive lens-wearing marmosets, the open symbols represent data from the negative lens-wearing marmosets and the crosses represent data from the plano lens-wearing marmosets. The ordinate scale is approximately equivalent to the ordinate scales in Figs. 1 and 2, using the approximate ratio of change in vitreous chamber depth to change in refraction calculated from the schematic eye for marmosets (Troilo, Howland, & Judge, 1993). Eyes wearing negative lenses showed increased axial growth relative to fellow eyes and eyes wearing positive lenses slowed in axial growth relative to fellow eyes.

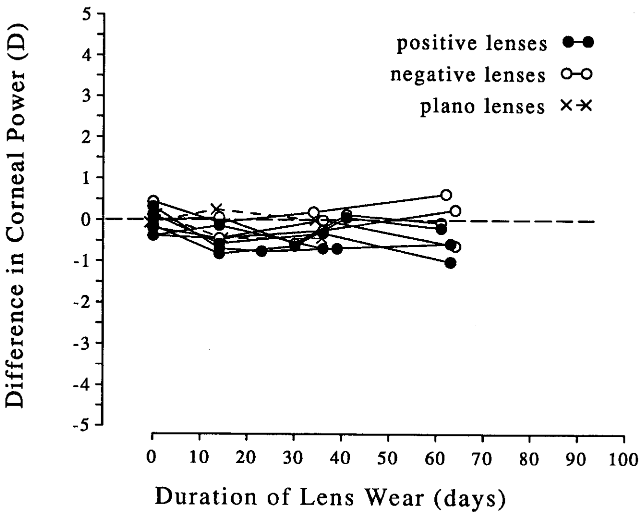

Fig. 3. Interocular difference in corneal power (lens-wearing eye — control eye) throughout the period of lens wear for all marmosets. Corneal power is in Dioptres and age is in days, plotted on a linear scale. The filled symbols represent data from the positive lens-wearing marmosets, the open symbols represent data from the negative lens-wearing marmosets and the crosses represent data from the plano lens-wearing marmosets.

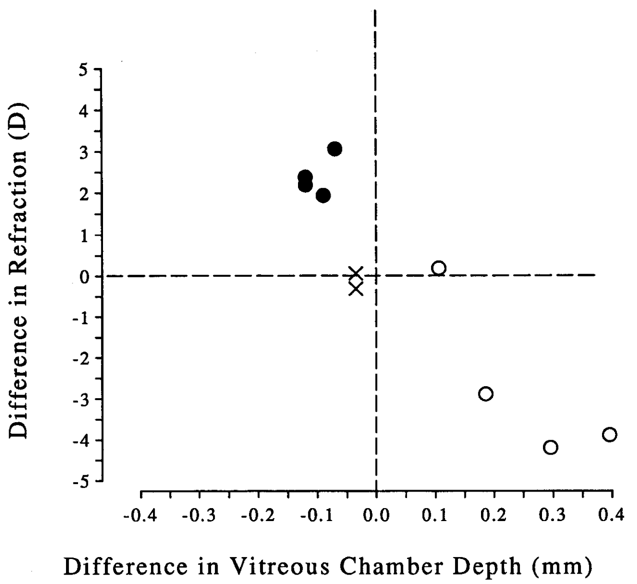

Fig. 4. Interocular difference in refraction (lens-wearing eye — control eye) is plotted against interocular difference in vitreous chamber depth (lens-wearing eye — control eye) for all marmosets at the end of the lens wear period. Refraction is in Dioptres and vitreous chamber depth is in millimetres. The two scales are approximately equivalent in Dioptres (1 mm interocular difference in VCD is approximately equivalent to an interocular difference in refraction of 12D). The filled symbols represent data from the positive lens-wearing marmosets, the open symbols represent data from the negative lens-wearing marmosets and the crosses represent data from the plano lens-wearing marmosets.

growth and refraction. At the end of the lens wear period there was no significant difference in refraction or vitreous chamber depth between the positive and negative lens-wearing groups (independent t-test on refractive error, $P = 0.59$; vitreous chamber depth, $P = 0.32$), nor was there any significant difference in refraction between these two groups throughout the period of lens wear (two factor ANOVA $P > 0.05$).

3.6. Plano lenses

Interocular differences in refractive error, vitreous chamber depth and corneal power throughout the lens-wear period for the two marmosets that wore plano lenses (He and Il) are shown in Fig. 1A, 2 and 3 by the diagonal cross symbols and dashed lines. Throughout the period of lens wear interocular differences in refraction or corneal power did not exceed 0.75D and interocular differences in vitreous chamber depth did not exceed 0.08 mm in either marmoset. Therefore there was no significant effect of contact lens wear per se on ocular growth and refractive development.

4. Discussion

4.1. Compensation to defocus imposed by contact lenses

Marmosets have been shown in the present study to develop changes in a compensatory direction to positive and negative soft contact lenses when the lenses are only worn for 8 h per day (for the full light period) on an 8:16 h light:dark cycle. The compensatory changes observed in the marmosets that wore powered contact lenses were not accompanied by significant changes in corneal power. Furthermore no significant changes in refraction, vitreous chamber depth and corneal power were observed in either marmoset fitted with a plano contact lens during the lens wear period. Therefore soft contact lenses, worn for only 8 h per day on an 8:16 h light:dark cycle, are a successful alternative to spectacle lenses for altering optical demand in experiments investigating the role of visual experience in regulating ocular growth and development. This is important because a successful contact lens wear paradigm allows experiments to be carried out on juvenile and early adult animals at an age which is more directly comparable to that at which humans frequently develop myopia.

4.2. Bidirectional compensation to defocus in young marmosets

This study has also demonstrated that marmoset eye growth and refraction can respond bidirectionally (i.e. hyperopia in response to positive lenses and myopia in response to negative lenses). All marmosets fitted with positive powered contact lenses developed hyperopic shifts in refraction in their lens-wearing eyes during the period of lens wear and three of the four marmosets fitted with negatively powered lenses developed myopic shifts (> 1D of relative and absolute myopia) during the period of lens wear. These results are important because they show that marmosets can respond bidirectionally in a similar way to macaque monkeys (Smith & Hung, 1999). Compensatory responses to positive *spectacle* lenses have not been previously reported in marmosets Graham and Judge (1999b). In the earlier study by Graham and Judge (1999b) infant marmosets wore spectacle lenses from 4 to 8 weeks of age compared to the present study in which marmosets wore contact lenses from ≈ 10 to 17 weeks of age. Therefore compensatory responses may have been observed in the current study because the lenses were worn at a time when emmetropisation from neonatal hyperopia had taken place (Graham & Judge, 1999a).

4.3. Contacts versus spectacles

The results reported in the present study are similar to the results reported by Hung et al. (1995) and Smith and Hung (1999) in which macaque monkeys developed hyperopia and myopia in response to wear of unilateral positive and negative spectacle lenses respectively, and are to be contrasted with the results reported by Hung and Smith (1996) using extended wear contact lenses. This is important because it brings the results obtained with contact lenses into line with the results previously reported using spectacle lenses, showing that qualitatively similar results (bidirectional compensation) can be obtained using both methods of altering optical demand. Furthermore soft contact lenses may also be superior to spectacle lenses as a means of altering optical demand in animal models of refractive development, in non-human primates in particular. The compensatory responses in marmosets to powered contact lenses appear to be greater than the responses previously reported to unilateral wear of positive lenses (+ 4D) and approximately equivalent to the response reported to unilateral negative (− 4D) spectacle lenses (Graham & Judge, 1999b) — although it was not possible to compare these two groups statistically as the period of lens wear and the age at onset of lens wear differed between the two groups. Nevertheless contact lenses worn for 8 h per day (on an 8:16 h light/dark cycle) are, in our view, potentially superior to spectacle lenses in animal models because of their optical advantages including increased field of view, less magnification changes and smaller prismatic effect.

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